(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/112776 A2

(51) International Patent Classification[7]: A61K 31/202, 31/07, 31/122, 31/015, 31/01

(21) International Application Number:
PCT/GB2004/002707

(22) International Filing Date: 23 June 2004 (23.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0314624.8 23 June 2003 (23.06.2003) GB

(71) Applicant *(for all designated States except US)*: ADVANCED BIONUTRITION (EUROPE) LIMITED [GB/GB]; 15 Grafton Road, Worthing, West Sussex BN11 1QR (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CLAYTON, Diane [GB/GB]; Advanced Bionutrition (Europe) Limited, 15 Grafton Road, Worthing, West Sussex BN11 1QR (GB). RUTTER, Rebecca [GB/GB]; Advanced Bionutrition (Europe) Limited, 15 Grafton Road, Worthing, West Sussex BN11 1QR (GB).

(74) Agent: HARRISON GODDARD FOOTE; 31 St. Saviourgate, York YO1 8NQ (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INFLAMMATORY DISEASE TREATMENT

(57) Abstract: We describe a composition comprising a source of long chain polyunsaturated fatty acid, for example, docosahexaenoic acid (DHA), and a carotenoid, for example, astaxanthin and other nutrients for prophylactic and/or therapeutic use in the healing of trauma- and stress-induced inflammatory conditions.

WO 2004/112776 A2

INFLAMMATORY DISEASE TREATMENT

The invention relates to a composition comprising a source of long chain polyunsaturated fatty acids, for example, docosahexaenoic acid (DHA), and a carotenoid, for example, astaxanthin, and other nutrients for prophylactic and/or therapeutic use in the healing of trauma- and stress-induced inflammatory conditions.

Background to the invention

Inflammation is a complex stereotypical reaction of the body responding to damage of its cells and vascularised tissues. The damaged sites are susceptible to infiltration by a multitude of pathogens including viruses, bacteria, fungi, and protozoan and metazoan parasites, as well as cancerous cells and other harmful agents and so the animal defends itself by initiating an inflammatory reaction at the damaged site.

The inflammatory reaction is phylogenetically and ontogenetically the oldest defence mechanism and both the innate and adaptive immune systems in vertebrates are triggered to destroy the infectious agent(s). When a tissue has been traumatised, for example, by injury or surgery, and is thus susceptible to infection, three key steps in the inflammatory response are initiated; (1) vasodilation, which enables an increased blood supply to the traumatised tissue; (2), increased capillary permeability caused by retraction of the endothelial cells allowing soluble mediators of immunity to reach the site of inflammation; and (3) migration of leukocytes (neutrophils; monocytes and lymphocytes) out of the capillaries into the surrounding tissues.

The development of inflammatory reactions is controlled in part by pro-inflammatory cytokines (e.g. interleukin-1, tumour necrosis factor alpha); by lipid mediators released from different cells (e.g. prostaglandin's and leukotrienes); by cell-derived vasoactive mediators released from mast cells, basophils and platelets (e.g. arachidonic acid metabolites; platelet activating factors amines: serotonin, histamine; endothelins) and by plasma-derived vasoactive mediators (e.g. kinins and components of the complement, coagulation and fibrinolytic cascades).

Chronic inflammation is an inflammatory response of prolonged duration - weeks, months, or even indefinitely - whose extended time course is provoked by the persistence of the causative stimulus to inflammation within the tissue. The inflammatory process inevitably causes tissue damage and is accompanied by misdirected attempts at simultaneous healing and repair. The exact nature, extent and time course of chronic inflammation is variable, and depends on a balance between the causative agent and the attempts of the body to remove it.

Chronic inflammation may develop either as a progression from acute inflammation if the original stimulus persists, or after repeated episodes of acute inflammation or *de novo* if the causative agent produces only a mild acute response.

Aetiological agents producing chronic inflammation include, but are not limited to: infectious organisms that can avoid or resist host defences and so persist in the tissue for a prolonged period; infectious organisms that are not innately resistant but persist in damaged regions where they are protected from host defences; irritant non-living foreign material that cannot be removed by enzymatic breakdown or phagocytosis; or where the stimuli is a "normal" tissue component, causing an auto-immune disease.

There is a vast array of diseases exhibiting a chronic inflammatory component. These include but are not limited to: inflammatory joint diseases (e.g., rheumatoid arthritis, osteoarthritis, polyarthritis and gout), chronic inflammatory connective tissue diseases (e.g., lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis, mixed connective tissue disease (MCTD), tendonitis, synovitis, bacterial endocarditis, osteomyelitis and psoriasis), chronic inflammatory lung diseases (e.g., chronic respiratory disease, pneumonia, fibrosing alveolitis, chronic bronchitis,chronic obstructive pulmonary disease (COPD), bronchiectasis, emphysema, silicosis and other pneumoconiosis and tuberculosis), chronic inflammatory bowel and gastro-intestinal tract inflammatory diseases (e.g., ulcerative colitis and Crohn's disease), chronic neural inflammatory diseases (e.g., chronic inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Guillan-Barre Syndrome and myasthemia gravis), other inflammatory diseases (e.g., mastitis, laminitis, laryngitis, chronic cholecystitis, Hashimoto's thyroiditis, inflammatory breast disease); chronic

inflammation caused by an implanted foreign body in a wound; and acute inflammatory tissue damage due to muscle damage after eccentric exercise (e.g., delayed onset muscle soreness – DOMS).

The usual mode of treatment for chronic inflammatory conditions is by administration of non-steroidal anti-inflammatory drugs (NSAID's) such as Diclofenac, Ibuprofen, Aspirin, Phenylbutazone, Indomethacin , Naproxen and Piroxicam. Although NSAID's can be effective, they are known to be associated with a number of side effects and adverse reactions. These may include gastro-intestinal problems such as dyspepsia, ulceration and haemorrhage, sleepiness, nausea or vomiting, constipation, allergic reactions and occasionally hepatoxicity. Frequently the margin between effective dose and toxic dose is quite small (i.e., 2-3 –fold). In spite of these side effects, the use of NSAID's as anti-inflammatory agents is standard practice in human medicine and veterinary medicine. However, within veterinary medicine there is an increasing concern about their use in food animals because of the potential for accumulation of drugs such as phenylbutazone within the food chain.

It is the purpose of this invention to provide a natural alternative to anti-inflammatory drugs widely used to treat chronic inflammatory conditions of terrestrial animals including humans. The use of such an alternative will be safe and without side-effects or risks to the environment.

DHA is an omega-3 fatty acid and is the most abundant long chain polyunsaturated fatty acid (PUFA) in the grey matter of the brain and other neurological tissues. Omega-3 PUFAs, particularly eicosapentaenoic acid (EPA) are known to be beneficial in reducing incidence of coronary heart disease (Lands, Fish and Human Health 1986 Academic Press). The anti-inflammatory properties of omega-3 PUFAs are thought to be provided by their ability to replace arachidonic (ARA) acid in immune cells membranes. ARA, an omega-6 PUFA with 20 carbon atoms and 4 double bonds (C20:4), is the biochemical precursor for the production of 2-series prostaglandins and 4-series leukotrienes associated with a range of pro-inflammatory molecules and mediators and can therefore impact pathogenesis of inflammatory diseases. (P. Calder "n-3 Fatty Acids & Health Conference (December 1999) British Nutrition Foundation). EPA, an omega-3 PUFA with 30 carbon atoms and 5 double

bonds (C20:5) is the biochemical precursor for the production of 3-series prostaglandins and 2-series leukotrienes which are anti-inflammatory molecules. Thus, the balance of EPA and ARA is thought to significantly affect the balance of pro- and anti-inflamatory eicosanoid mediators. DHA, an omega-3 PUFA with 22 carbon atoms and 6 double bonds (C22:6) does not form eicosanoids (i.e., 20C prostaglandins or leukotrienes). Omega-3 fatty acids have a long history of use in animal feeding via use of cod liver oil, linseed and flax oil.

A metabolic pathway exists in mammals for the biosynthesis of DHA, but this is bio-energetically unfavourable (Crawford, P. AOCS, Short Course in Polyunsaturated Fatty Acids and Eicosanoids, pp270-295 (1987)). The metabolism of omega-3 fatty acids is not well understood, thus precise clinical dosage rates and efficacy remain unknown. Mammals are thought to obtain most of their DHA from dietary sources.

Omega-3 and omega-6 fatty acids are found in cold-water marine fish; and fish oils are the primary commercial source of these fatty acids. Environmental pollution of fish introduces toxic factors such as dioxins and PCB's to the oils recovered from fish, which if ingested may adversely affect the health of all animals and may remain as residues in food animals rendering them problematic for human consumption.

Marine microorganisms are known to contain DHA, in particular dinoflagellates (Harrington et al "The Polyunsaturated Fatty Acids of Marine Dinoflagellates" J. Protozoal, 17:213-219 (1970)). Successful cultivation of these in commercial conditions is achievable (U.S 5,407,957). In adequate presence of Vitamin E up to animals can consume up to 2% of their diet as DHA when using fish oil, but higher levels result in malodorous products.

Astaxanthin is a carotenoid known to be partially degraded in the gastro-intestinal tract by oxidation. The presence of vitamins A, C, selenium, manganese, zinc and copper are known to alleviate this effect. Certain microorganisms including but not limited to algae and yeast are know to be prolific producers of astaxanthin. Both forms of algae, and yeast contain adequate combinations of the above elements to counteract the oxidative effect of digestive oxidation to both the lipids and the astaxanthin therein.

Other marine organisms, including but not limited to zooplankton, crustaceans, molluscs, and vertebrates, are also known to contain high levels of the carotenoid astaxanthin. It has been shown that in fish and crustaceans, astaxanthin is essential for growth and plays a vitamin-like role. Astaxanthin also appears to have some beneficial effects on mammals. Astaxanthin is an active ingredient in several patented medications for mammals. In an anti-stress formulation, it is claimed to enhance the effect of anti-stress agents administered to farm animals and household pets to minimise weight loss and reduced immunity due to crowding, extreme temperatures and other sudden environmental changes (U.S 5,937,790).

Esterified astaxanthin from the alga *Haematococcus pluvialis* is the preferred form in several oral prophylactic and therapeutic formulations for muscular dysfunction such as exertional rhabdomyolysis (also known as exertional myopathy, tying-up syndrome, azoturia, or Monday morning sickness) in horses (WO 99/11251), as well as for mastitis (mammary inflammation) in dairy cows (WO 98/30701), and for mammalian gastrointestinal tract inflammation due to infections by *Helicobacter* sp. bacteria (WO 98/37874).

The use of yeast in animal feed has a long and well-documented history. Recent changes to European law (EC Directive 87/153/EEC and associated reports) specifically in respect to the ability of a gastro-intestinal tract to resist overgrowth by any one component or strain is now active. Whilst the mode of action is not documented, it is thought that there are similarities between the action of the rumen and the cecal fermentation of mammals that rely on bacterial fermentation resulting in production of lactic acid. (Martin, S.A. and Nisbet, D.J., "Effect of direct-fed microbials on rumen microbial fermentation" J. Dairy Sci. 75:1736 (1992))

Recent research and meta-analysis shows yeast to improve digestion and availability of nutrients when nutritional demands are high. Positive effects on the efficacy of immune systems to increase macrophage activity against *E. coli* and *Salmonella typhirium* have been shown. (Hatcher G. E., Lambretch R.S., "Augmentation of macrophage phagocytic activity by cell-free extracts of selected lactic acid producing bacteria" J. Dairy Sci. 76:2485 (1993) and Schiffrin, E.J. et al, "Immunomodulation

of human blood cells following the ingestion of lactic acid bacteria J. Dairy Sci 78:491 (1995))

An object of the present invention is to provide a dietary supplement to an animal, including humans, that will provide a protective benefit against inflammation (particularly to animals in high stress environments such as, but not limited to competition or transportation), and/or to be used therapeutically to further enhance the healing of trauma and stress-induced inflammatory conditions.

A further objective of this invention is to provide a natural alternative to anti-inflammatory drugs currently used in traditional veterinary and human medicine.

We have found that a combination of an omega-3 PUFA and astaxanthin provides an unexpectedly beneficial effect in reducing the negative effects of inflammatory processes, and further that these materials can be provided to an animal, including humans, in a natural and bioavailable form.

Summary of the Invention

According to an aspect of the invention there is provided a composition comprising at least one long chain polyunsaturated fatty acid and at least one carotenoid.

In a preferred embodiment of the invention said long chain fatty acid is a free fatty acid, or an ester thereof.

In a further preferred embodiment of the invention said long chain fatty acid is selected from the group consisting of: a triglyceride, diglyceride, monoglyceride, phospholipids, glycolipid, sphingolipid or sulpholipid.

In a further preferred embodiment of the invention said long chain fatty acid is docosahexaenoic acid.

In a preferred embodiment of the invention said docosahexaenoic acid is provided as an edible algae. Preferably said edible algae is selected from the group consisting of, but not limited to: *Crypthecodinium; Phaedactylum; Isochrysis; Schizochytrium; Thaustochytrium;* or *Ulkenia.*

In a preferred embodiment of the invention said long chain fatty acid is eicosapentaenoic acid.

In a preferred embodiment of the invention said eicosapentaenoic acid is provided as an edible algae. Preferably said edible algae is selected from the group consisting of, but not limited to: *Isochrysis; Nannochloris, Cyclotella, Phaeodactylum,* or *Navicula,*

In a yet further preferred embodiment of the invention said carotenoid is astaxanthin.

In a yet further preferred embodiment of the invention astaxanthin is provided as an edible algae or yeast.

In a preferred embodiment of the invention said composition further comprises yeast.

In a further preferred embodiment of the invention said composition further comprises a further anti-inflammatory or antioxidant agent.

In a preferred embodiment of the invention said further anti-inflammatory or antioxidant agent is selected from the group consisting of, but not limited to: vitamin C, vitamin E, lycopene, ß-carotene, lutein, organic selenium, α-lipoic acid, glycine, taurine, methylsulfonylmethane, glutamine, arginine, cysteine, methionine, S-adenosylmethionine, nucleotides, nucleic acids, curcumin, green tea extract, green-lipped mussel extract (*Perna canaliculus*) or standardised herbal extracts such as *Phyllanthus amarus* , *Fructus Schisandra*, Chamomile, Blackcurrant leaf or Devil's claw.

According to a further aspect of the invention there is provided a composition according to any previous aspect or embodiment for use as a nutraceutical.

When administered, compositions of the present invention are administered in physiologically acceptable preparations. Such preparations may routinely contain physiologically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers and optionally other therapeutic agents.

The compositions of the invention can be administered by any conventional route, including, but not limited to, injection, or gradual infusion over time. The administration may, for example, be oral, intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. Preferably said compositions are administered orally in the feed or as a feed supplement. Alternatively, the compositions can be provided in the water or as a tonic.

The compositions of the invention are administered in effective amounts. An "effective amount" is that amount of a composition that alone, or together with further doses, produces the desired response. In the case of treating a particular disease, such as arthritis, the desired response is inhibiting the progression of the disease. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by routine methods.

Such amounts will depend, of course, on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. The compositions used in the foregoing methods preferably are sterile and contain an effective amount of the active agents for producing the desired response in a unit of weight or volume suitable for administration to a patient.

In general, the active agent DHA is formulated and administered in doses between 0.05-500mg/kg body weight, preferably between 0.5-15 mg/kg body weight, and most preferably between 1-3mg /kg body weight. The active agent astaxanthin is formulated and administered in doses between 0.0005mg–5mg/kg body weight,

preferably between 0.0015-0.15mg/kg body weight, and most preferably between 0.0075-0.0225mg/kg body weight according to any standard procedure in the art.

Compositions may be combined, if desired, with a physiologically-acceptable carrier. The term "physiologically-acceptable carrier" as used herein means one or more compatible solid or liquid fillers, diluents or encapsulating substances that are suitable for administration into a human or animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The compositions may contain suitable buffering agents.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well-known in the food industry for the preparation of food and food supplements, or by methods known to the pharmaceutical industry. Methods known to those skilled in the art of food manufacturing include but are not limited to dry-blending of active agents and other ingredients in powder form , spray-drying of emulsions containing all components or the use of extrusion technologies to form pellets or granules .

Pharmaceutical methods include the step of bringing the active agent into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product. This can then be either administered directly to the animal or added to food.

Compositions suitable for oral administration may be presented as discrete units, such as capsules, tablets, lozenges, each containing a predetermined amount of the active agent. Other compositions include suspensions in aqueous liquids or non-aqueous liquids such as a syrup, elixir, tonic, or an emulsion.

According to a further aspect of the invention there is provided the use of a composition according to the invention for the manufacture of a nutraceutical for use in the treatment of inflammatory conditions.

In a preferred embodiment of the invention said inflammatory condition is selected from the group consisting of, but not limited to: inflammatory joint diseases (e.g. rheumatoid arthritis, osteoarthritis, polyarthritis and gout); chronic inflammatory connective tissue diseases (e.g. lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis) ; mixed connective tissue disease (MCTD) (e.g. tendonitis, synovitis, bacterial endocarditis, osteomyelitis and psoriasis); chronic inflammatory lung diseases (e.g. chronic respiratory disease, pneumonia, fibrosing alveolitis, chronic bronchitis, chronic obstructive pulmonary disease (COPD) , bronchiectasis, emphysema, silicosis and other pneumoconiosis and tuberculosis); chronic inflammatory bowel and gastro-intestinal tract inflammatory diseases (e.g. ulcerative colitis and Crohn's disease); chronic neural inflammatory diseases (e.g. chronic inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Guillan-Barre Syndrome and myasthemia gravis); and other inflammatory diseases including, mastitis, laminitis, laryngitis, chronic cholecystitis, Hashimoto's thyroiditis, inflammatory breast disease; chronic inflammation caused by an implanted foreign body in a wound; and acute inflammatory tissue damage due to muscle damage after eccentric exercise (e.g., delayed onset muscle soreness – DOMS).

According to a further aspect of the invention there is provided a food stuff wherein said food stuff comprises a composition according to any previous aspect of embodiment.

According to a further aspect of the invention there is provided a method to treat an animal suffering from an inflammatory condition or disease comprising administering to said animal an effective amount of at least one long chain polyunsaturated fatty acid and at least one carotenoid.

In a preferred method of the invention said long chain fatty acid is a free fatty acid, or an ester thereof.

In a further preferred method of the invention said long chain fatty acid is selected from the group consisting of: a triglyceride, diglyceride, monoglyceride, phospholipids, glycolipid, sphingolipid or sulpholipid.

In a further preferred method of the invention said long chain fatty acid is docosahexanoic acid.

In a yet further preferred method of the invention said carotenoid is astaxanthin.

In a further preferred method of the invention said animal is administered a further anti-inflammatory agent.

In a preferred method of the invention said disease or condition is selected from the group consisting of but not limited to: inflammatory joint diseases (e.g. rheumatoid arthritis, osteoarthritis, polyarthritis and gout); chronic inflammatory connective tissue diseases (e.g. lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis); mixed connective tissue disease (MCTD)(e.g. tendonitis, synovitis, bacterial endocarditis, osteomyelitis and psoriasis); chronic inflammatory lung diseases (e.g. chronic respiratory disease, pneumonia, fibrosing alveolitis, chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, emphysema, silicosis and other pneumoconiosis and tuberculosis); chronic inflammatory bowel and gastro-intestinal tract inflammatory diseases (e.g. ulcerative colitis and Crohn's disease); chronic neural inflammatory diseases (e.g. chronic inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Guillan-Barre Syndrome and myasthemia gravis); and other inflammatory diseases including, mastitis, laminitis, laryngitis, chronic cholecystitis, Hashimoto's thyroiditis, inflammatory breast disease; chronic inflammation caused by an implanted foreign body in a wound; and acute inflammatory tissue damage due to muscle damage after eccentric exercise (e.g., delayed onset muscle soreness – DOMS).

In a preferred method of the invention said animal is a terrestrial animal

In a further preferred method of the invention said animal is a companion or performance animal.

In a further preferred method of the invention said animal is selected from the group consisting of: human, horse, cow; sheep; goat; llama, camel, mink; pig; dog; cat; hamster; mouse; rabbit; pot bellied pig; rat, gerbil, guinea pig.

In a preferred method of the invention said animal is a horse.

In a further preferred method of the invention said animal is a human.

An embodiment of the invention will now be described by example only and with reference to the following materials, methods and examples.

Materials and Methods

Sources of DHA and astaxanthin:

DHA can be found in oils extracted from marine animals and organisms, including algae. Suitable commercial sources of DHA include, but are not limited to algae such as *Crypthecodinium; Phaedactylum; Isochrysis*; *Schizochytrium; Thaustochytrium;* or *Ulkenia*, or purified, or semipurified lipid products from these species.

Alternatively DHA can be provided by commercially available marine oils which typically contain levels between 15% and 25% DHA and between 5% and 15% EPA (w/w). Suitable marine oils include, but are not limited to: crude or processed fish oil, krill oil, squid oil, or refining or processing coproducts from the manufacture of these oils.

Suitable sources of commercially available astaxanthin include, but are not limited to: the dried algae product *Haematococcus pluvialis* (Cyanotech Corp, USA), dehydrated yeast product *Phaffia rhodozyma* (Igene Corp, USA). Alternatively the commercially available synthetic form of astaxanthin may be used (Roche, Switzerland; BASF, Germany).

Manufacture of pellets for animal feeds :

Ingredients as described in the examples below (formulas 1-18) are dry-blended together with oatmeal, grass meal , calcium carbonate, liquid oat oil and a suitable pellet binder. The mixture is processed using cool extrusion technology as routinely used by those skilled in the art of food manufacture.

Most preferred levels of inclusion of fomulas 1-18 typically range from 5-40%

Manufacture of soft gel capsules suitable for human consumption:

Suitable inner filling components are described by, but not limited to , formulas 19-21 and formulas 25-26. A liquid premix , prepared with optional use of emulsifiers and stabilising agents comprises about 70% by weight of the capsule. The outer shell of the capsule (approx. 30% total capsule weight) comprises predominantly gelatin or a vegetable gum alternative as well as glycerol and flavouring/colouring components.

TABLE 1. EXAMPLES OF SUITABLE FORMULAE FOR PRODUCT MANUFACTURE

Formula 1.

Ingredient	**%**
Crypthecodinium cohnii (dried biomass)	60
Haematococcus (dried biomass)	5
Inactivated Brewers dried yeast	35

Formula 2.

Ingredient	**%**
Crypthecodinium cohnii (dried biomass)	40.0
Haematococcus (dried biomass)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	33.3

Formula 3.

Ingredient	%
Schizochytrium sp. (dried biomass)	60
Haematococcus (dried biomass)	5
Inactivated Brewers dried yeast	35

Formula 4.

Ingredient	%
Schizochytrium sp.(dried biomass)	40.0
Haematococcus (dried biomass)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	33.3

Formula 5

Ingredient	%
Crypthecodinium cohnii (dried biomass)	60.0
Astaxanthin (Pfaffia)	5
Inactivated Brewers dried yeast	35

Formula 6.

Ingredient	%
Crypthecodinium cohnii (dried biomass)	60.0
Astaxanthin (synthetic)	5
Inactivated Brewers dried yeast	35

Formula 7.

Ingredient	%
Crypthecodinium cohnii (dried biomass)	40.0
Astaxanthin (Pfaffia)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	33.3

Formula 8.

Ingredient	%
Crypthecodinium cohnii (dried biomass)	40.0
Astaxanthin (synthetic)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	33.3

Formula 9.

Ingredient	%
Schizochytrium sp. (dried biomass)	60
Astaxanthin (Pfaffia)	5
Inactivated Brewers dried yeast	35

Formula 10.

Ingredient	%
Schizochytrium sp. (dried biomass)	60
Astaxanthin (synthetic)	0.05
Inactivated Brewers dried yeast	35
Grass Meal	4.95

Formula 11.

Ingredient	%
Schizochytrium sp.(dried biomass)	40.0
Astaxanthin (Pfaffia)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	33.3

Formula 12.

Ingredient	%
Schizochytrium sp.(dried biomass)	40.0
Astaxanthin (synthetic)	0.05
Inactivated Brewers dried yeast	23.3
Grass Meal	36.65

Formula 13.

Ingredient	%
Fish oil (microencapsulated)	75
Haematococcus (dried biomass)	3
Inactivated Brewers dried yeast	22

Formula 14.

Ingredient	%
Fish oil (microencapsulated)	75
Pfaffia (astaxanthin)	3
Inactivated Brewers dried yeast	22

Formula 15.

Ingredient	%
Fish oil (microencapsulated)	75
Astaxanthin (synthetic)	0.05
Inactivated Brewers dried yeast	24.95

Formula 16.

Ingredient	%
Fish oil (microencapsulated)	75
Haematococcus (dried biomass)	3
Inactivated Brewers dried yeast	20
Grass Meal	2

Formula 17.

Ingredient	%
Fish oil (microencapsulated)	75
Astaxanthin (Pfaffia)	3
Inactivated Brewers dried yeast	20
Grass Meal	2

Formula 18.

Ingredient	%
Fish oil (microencapsulated)	75
Astaxanthin (synthetic)	3
Inactivated Brewers dried yeast	20
Grass Meal	2

Formula 19.

Ingredient	%
DHA algal oil (DHASCO)®	15
Haematococcus (dried biomass)	15
Inactivated Brewers dried yeast	35
Other ingredients	To 100

Formula 20.

Ingredient	%
DHA algal oil (DHASCO)®	15
Astaxanthin (Pfaffia)	3
Inactivated Brewers dried yeast	35
Other ingredients	To 100

Formula 21.

Ingredient	%
DHA algal oil (DHASCO)®	15
Astaxanthin (synthetic)	0.045
Inactivated Brewers dried yeast	35

Other ingredients	To 100

Formula 22.

Ingredient	**%**
DHA algal oil (DHASCO)®	15
Haematococcus (dried biomass)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	25.3
Other ingredients	To 100

Formula 23.

Ingredient	**%**
DHA algal oil (DHASCO)®	15
Astaxanthin (Pfaffia)	3.4
Inactivated Brewers dried yeast	23.3
Grass Meal	25.3
Other ingredients	To 100

Formula 24.

Ingredient	**%**
DHA algal oil (DHASCO)®	15
Astaxanthin (synthetic)	0.1
Inactivated Brewers dried yeast	23.3
Grass Meal	25.3
Other ingredients	To 100

Formula 25.

Ingredient	**%**
DHA (Any source)	20
Astaxanthin (any source)	0.15
α-Lipoic acid	0.2
Natural flavours	0.3

Maltodextrin 20 DE	To 100

Formula 26.

Ingredient	%
DHA (Any source)	20
Astaxanthin (any source)	0.15
Methyl sulfonyl methane (any source)	0.2
Natural flavours	0.3
Maltodextrin 20 DE	To 100

EXAMPLE 1

Case Study 1

A 26-year-old, 15.2hh ¾ thoroughbred gelding had undergone metacarpal surgery on his off-fore knee 15 months prior to intervention. The animal was suffering osteoarthritis, general stiffness more deterioration in ability to movement when cold. Long-term soft tissue swelling at the site of the injury and surgery remained round knee joint decreasing possibility of flexion further. Oedema surrounding ligaments and tendons occurred upon inactivity (e.g. stabling)

Dietary intake had included a range of herbal supplements, but no chemical phenylbutazone or other anti-inflammatory substances; 95% forage based with 1kg per day cereal mix. Initial dose of 0.5g formula 1 per day was included in the diet, increasing over 14 days to 8g invention per day. Soft tissue swelling reduced above and below knee within 7 days (5mm decrease in circumference above knee and 4mm below knee), oedema reduced in hind lower limbs, stiffness on activity following rest was noticeably reduced. After 21 days general alertness and overall health was noticed to have improved, e.g. coat condition. Horse was more eager to canter in field and less prone to stumbling on off fore.

EXAMPLE 2

Case Study 2

The subject was a 23-year-old, 13.2hh cob mare exhibiting old age related stiffness, notably following work on hard ground and when weather was cold and wet. Clinical

symptoms were reluctance to move quickly whether ridden or in-hand, stiffness when moving out of stable following period of inactivity, oedema in lower limbs, slight grumpy manner when being handled and reluctance to engage in spontaneous movement in field. General health was good. Diet was 95% forage based, with small amount of soaked sugar beet pulp per day. No drug therapy was used, but pony has previously received phenylbutazone for stiffness and swellings.

Initial dose of 5g formula 1 per day for 5 days showed dramatic improvement with eagerness to move both ridden, in-hand and when free. Energy levels increased with improvement in disposition when handled, pony started to jump out of field over 1 metre 10cm high fence which previously was impossible for her, stride length of hind limbs increased to allow hoof prints of front hooves to be covered by hind hooves. Dose reduced to 2.5g per day, improvements still noticeable and oedema in lower limbs reduced. Maintenance dose of 2g invention per day showed no loss of activity. Comments on improvement in action, attitude and ability of pony noted by owner, farrier and instructor, none of whom were aware of the dietary changes made.

EXAMPLE 3

Case Study 3

Subject was a 11-year-old 12hh show pony suffering from laminitis, and not ridden due to chronic lameness, possibly due to muscle, shoulder injury sustained 22 months prior to test. No improvement when given phenylbutazone or other anti-inflammatory substances, difficult for farrier to work on as pony unable to move leg away from body at an angle; could not hold balance with foot off ground and was very stiff and sore for 2 to 5 days following attention from farrier, a result of the injury. 95% forage based diet with 1kg cereal inclusion per day, turn out in field but no exercise. Pony very stiff at all times, movement across uneven terrain difficult, not able to be ridden.

Initial dose of 2.5g formula 1 per day for 5 days showed dramatic improvement with pony much freer in action. Pony jumped out of field over 1meter 10cm fencing, landing on hard ground and was still sound, even the next day. After 4 weeks farrier shod pony and used him as an example to train other farriers because of his history of laminitis. Pony's ability to move leg, shoulder and withstand repeated lifting of legs was totally unexpected. Maintenance dose of 2g per day was used thereafter.

EXAMPLE 4

Case Study 4

Subject was a 10-year-old King Charles Cavalier spaniel diagnosed with rheumatism in left hip, noticeable stiffness and inability to use hind limbs after exercise and worse in cold weather. Daily treatments with 0.5 g of formula 1 resulted in improvement in coat and ability to exercise without pain (lifting of leg, limping, stopping suddenly) within 4 days. Dose was dropped to 0.5g per day on alternate days after 10 days of initial treatment and the animal continued to improve.

EXAMPLE 5

Case Study 5

Subject was an 8 year old miniature Poodle, with general stiffness, unwillingness to jump on chairs, not using one hind limb when walking, notably stiff when getting up after rest, difficulty in using stairs of house and not playing with other dogs. Intervention with Formula 1 at a dose of 0.25g per day with food for 7 days showed marked improvement in dogs movement, ability to jump on chairs/laps, and speed of ascent and descent of stairs. Play with other dog was initiated and speed of game was increased. Level of dose was maintained with overall improvement in dog's quality of life seen and overall condition.

EXAMPLE 6

Case Study 6

Subject was a 12 year old event mare with long term recurrent check ligament injury and residual swelling. Injury would reoccur after return to work, when work rate and load increased to increase fitness in an intermittent pattern. Condition was manageable with phenylbutazone, but residual swelling was not altered by this regime. Long term prognosis was retirements from competition and use as light hack or brood mare only, as competition laws do not allow use of non-steroidal anti-inflammatory substances. Intervention with Formula 2 at 0.25g per day increasing to a maximum daily load of 1g per day showed swelling reduced, intermittent lameness ceased; mare returned to full work load and regained competitive fitness levels

without recurrence of injury. Mare is now competing again in Eventing and other sports.

EXAMPLE 7

Case Study 7

Subject was a 4 year old 16.2hh Irish Sports Horse who developed a splint on near fore measuring 6mm diameter; showing some signs of lameness, heat in splint formation and swelling in surrounding tendon sheaths. Vet recommended rest, treatment with phenylbutazone and cold hosing for 8 to 16 weeks with return to light work over period of 4 months if all signs of swelling had gone.

Phenylbutazone was not a preferred choice by the owner, so this was substituted by intervention with formula 2 at a dose of 8g per day. By Day 3 of intervention residual swelling in tendon sheaths had decreased, some remaining. Size of splint had decreased by 2mm diameter, all heat in splint was gone. After Day 8 treatment was suspended, and within 24 hours heat returned to splint, size increased back to 8mm and continued to increase on Day 9. Treatment was resumed on day 10, by Day 14 splint was cold and size reducing again. Treatment ongoing for minimum 14 days to settle splint formation, reduce heat and associated swelling.

CLAIMS

1. A nutraceutical for use in the treatment of inflammatory conditions comprising docosahexaenoic acid or an ester thereof and at least one carotenoid.

2. The nutraceutical according to Claim 1 wherein the ester of docosahexaenoic acid is selected from the group consisting of: a triglyceride, diglyceride, monoglyceride, phospholipids, glycolipid, sphingolipid or sulpholipid.

3. The nutraceutical of Claims 1 or 2 wherein said docosahexaenoic acid is provided as an algae or fraction thereof.

4. The nutraceutical of Claim 3 wherein said algae is selected from the group consisting of: *Crypthecodinium; Phaedactylum; Isochrysis*; *Schizochytrium; Thaustochytrium;* or *Ulkenia.*

5. The nutraceutical of Claims 1 or 2 wherein said docosahexaenoic acid is provided as a fish oil or fraction thereof.

6. The nutraceutical according to any of Claims 1-5 wherein said carotenoid is selected from the group consisting of astaxanthin, zeaxanthin, lycopene, lutein, or carotene.

7. The nutraceutical according to any of Claims 1-6 wherein said carotenoid is from a microbial source.

8. The nutraceutical according to Claim 7 wherein said microbe is *Haematococcus* or *Pfaffia.*

9. The nutraceutical according to any of Claims 1-8 wherein said docosahexaenoic acid is provided to an animal at a dose of between 0.05 and 500 mg/kg body weight and said carotenoid is provided at a dose of between 0.5 and 5,000 ug/kg body weight.

10. The nutraceutical according to any of Claims 1-8 wherein said docosahexaenoic acid is provided to an animal at a dose of between 0.5 and 15 mg/kg body weight and said carotenoid is provided at a dose of between 1.5 and 150 ug/kg body weight.

11. The nutraceutical according to any of Claims 1-8 wherein said docosahexaenoic acid is provided to an animal at a dose of between 1 and 3 mg/kg body weight and said carotenoid is provided at a dose of between 7.5 and 22.5 ug/kg body weight.

12. The nutraceutical according to any of Claims 1-11 wherein said composition further comprises yeast.

13. The nutraceutical according to any of Claims 1-12 wherein said composition further comprises an anti-inflammatory agent.

14. The nutraceutical according to Claim 13 wherein said further anti-inflammatory agent is selected from the group consisting of: vitamin C, vitamin E, lycopene, ß-carotene, lutein, organic selenium, α-lipoic acid, methylsulfonylmethane, glutathione, taurine, glycine, glutamine, arginine, cysteine, methionine, S-adenosylmethionine, nucleotides, nucleic acids, curcumin, green tea extract, green-lipped mussel extract (Perna canaliculus), or standardised herbal extracts such as *Phyllanthus amarus*, *Fructus Schisandra* , Chamomile, Blackcurrant leaf, Devil's claw.

15. The nutraceutical according to any of Claims 1-14 wherein said inflammatory condition is selected from the group consisting of: inflammatory joint diseases e.g. rheumatoid arthritis, osteoarthritis, polyarthritis and gout; chronic inflammatory connective tissue diseases e.g. lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis; mixed connective tissue disease (MCTD), e.g. tendonitis, synovitis, bacterial endocarditis, osteomyelitis and psoriasis; chronic inflammatory lung diseases e.g. chronic respiratory disease, pneumonia, fibrosing alveolitis, chronic bronchitis,chronic obstructive pulmonary disease (COPD), bronchiectasis, emphysema, silicosis and other pneumoconiosis and tuberculosis; chronic inflammatory bowel and gastro-intestinal tract inflammatory diseases e.g. ulcerative colitis and Crohn's disease; chronic neural inflammatory diseases e.g. chronic inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Guillan-Barre Syndrome and myasthemia gravis; and including, mastitis, laminitis,

laryngitis, chronic cholecystitis, Hashimoto's thyroiditis, inflammatory breast disease, and chronic inflammation.

16. A composition comprising an algal source of docosahexaenoic acid and a microbial source of astaxanthin.

17. The composition of Claim 16 wherein the algae is selected from the group consisting of: *Crypthecodinium; Phaedactylum; Isochrysis*; *Schizochytrium; Thaustochytrium;* or *Ulkenia*,

18. The composition of Claim 16 or 17 wherein the microbial source of astaxanthin is *Haematococcus* or *Pfaffia*.

19. The composition of Claims 16-18 further comprising inactivated brewers yeast.

20. The composition of any of claims 16-19 further comprising an anti-inflammatory agent selected from the group consisting of: vitamin C, vitamin E, lycopene, ß-carotene, lutein , organic selenium, α-lipoic acid, methylsulfonylmethane, glutathione, taurine, glycine, glutamine, arginine, cysteine, methionine, S-adenosylmethionine, nucleotides, nucleic acids, curcumin, green tea extract, green-lipped mussel extract (Perna canaliculus), or standardised herbal extracts such as Phyllanthus amarus, Fructus Schisandra , Chamomile, Blacurrant leaf, Devil's claw.

21. A feed comprising the nutraceutical according to any of Claims 1-15.

22. A feed comprising the nutraceutical according to any of Claims 1-15 and grass meal.

23. A method of treating an animal suffering from an inflammatory condition or disease comprising administering to said animal an effective amount of at least one long chain polyunsaturated fatty acid and at least one carotenoid.

24. A method according to Claim 23 wherein said long chain fatty acid is a free fatty acid, or an ester thereof.

25. A method according to Claim 23 or 24 wherein said long chain fatty acid is selected from the group consisting of: a triglyceride, diglyceride, monoglyceride, phospholipids, glycolipid, sphingolipid or sulpholipid.

26. A method according to any of Claims 23-25 wherein said long chain fatty acid is docosahexanoic acid.

27. A method according to any of Claims 23-26 wherein said carotenoid is selected from the group consisting of: astaxanthin, zeaxanthin, lycopene, lutein, or carotene.

28. A method according to any of Claims 23-27 wherein said animal is administered a further anti-inflammatory agent.

29. A method according to any of Claims 23-28 wherein said disease or condition is selected from the group consisting of: inflammatory joint diseases e.g. rheumatoid arthritis, osteoarthritis, polyarthritis and gout; chronic inflammatory connective tissue diseases e.g. lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis; mixed connective tissue disease (MCTD), e.g. tendonitis, synovitis, bacterial endocarditis, osteomyelitis and psoriasis; chronic inflammatory lung diseases e.g. chronic respiratory disease, pneumonia, fibrosing alveolitis, chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchiectasis, emphysema, silicosis and other pneumoconiosis and tuberculosis; chronic inflammatory bowel and gastro-intestinal tract inflammatory diseases e.g. ulcerative colitis and Crohn's disease; chronic neural inflammatory diseases e.g. chronic inflammatory demyelinating polyradiculoneuropathy, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Guillan-Barre Syndrome and myasthemia gravis; and including, mastitis, laminitis, laryngitis, chronic cholecystitis, Hashimoto's thyroiditis, inflammatory breast disease; chronic inflammation (e.g., caused by an implanted foreign body in a wound); and acute inflammatory tissue damage due to muscle damage after eccentric exercise (e.g., delayed onset muscle soreness – DOMS).

30. A method according to any of Claims 23-29wherein said animal is selected from the group consisting of: horse; dog; cat ; cow; sheep; goat; camel, llama, mink; pig; hamster; mouse; rabbit; pot bellied pig; rat, gerbil, guinea pig.

31. A method according to any of Claims 23-29 wherein said animal is a human.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/112776 A3

(51) International Patent Classification[7]: A61K 31/202, 31/07, 31/122, 31/015, 31/01

(21) International Application Number:
PCT/GB2004/002707

(22) International Filing Date: 23 June 2004 (23.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0314624.8 23 June 2003 (23.06.2003) GB

(71) Applicant (*for all designated States except US*): ADVANCED BIONUTRITION (EUROPE) LIMITED [GB/GB]; 15 Grafton Road, Worthing, West Sussex BN11 1QR (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): CLAYTON, Diane [GB/GB]; Advanced Bionutrition (Europe) Limited, 15 Grafton Road, Worthing, West Sussex BN11 1QR (GB). RUTTER, Rebecca [GB/GB]; Advanced Bionutrition (Europe) Limited, 15 Grafton Road, Worthing, West Sussex BN11 1QR (GB).

(74) Agent: HARRISON GODDARD FOOTE; 31 St. Saviourgate, York YO1 8NQ (GB).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
31 March 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INFLAMMATORY DISEASE TREATMENT

(57) Abstract: We describe a composition comprising a source of long chain polyunsaturated fatty acid, for example, docosahexaenoic acid (DHA), and a carotenoid, for example, astaxanthin and other nutrients for prophylactic and/or therapeutic use in the healing of trauma- and stress-induced inflammatory conditions.

WO 2004/112776 A3

INTERNATIONAL SEARCH REPORT

International Application No
T/GB2004/002707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/202 A61K31/07 A61K31/122 A61K31/015 A61K31/01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 699 437 A (PROSPA BV) 6 March 1996 (1996-03-06) page 1, paragraph 2 page 1, line 29 page 4, paragraphs 4,5	1,6, 9-11,21, 23,24, 26,27,31
X	WO 02/102394 A (SAMPALIS TINA ; NEPTUNE TECHNOLOGIES & BIORESS (CA)) 27 December 2002 (2002-12-27) page 1, paragraph 3 page 2, line 22 - page 3, line 14 claims 28,29	1,6,14, 15,21, 23,24, 26,27, 29,31

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2005	20/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 444 054 A (DEMICHELE STEPHEN J ET AL) 22 August 1995 (1995-08-22) claims 10,11 table 3	1,3,5,6, 12-16, 19-21, 23,24, 26-29,31
X	WO 98/37874 A (ALEJUNG PAER ; ASTACAROTENE AB (SE); WADSTROEM TORKEL (SE)) 3 September 1998 (1998-09-03) cited in the application page 1, paragraph 1 claims	23,24, 27-29,31
Y	WO 01/24787 A (BOETTIGER PER ; ASTACAROTENE AB (SE); LIGNELL AAKE (SE)) 12 April 2001 (2001-04-12) claims	1-31
Y	GUERIN M ET AL: "Haematococcus astaxanthin: applications for human health and nutrition" TRENDS IN BIOTECHNOLOGY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 21, no. 5, May 2003 (2003-05), pages 210-216, XP004422156 ISSN: 0167-7799 page 212, column 2, paragraphs 2,3	1-31
Y	WANG X ET AL: "Astaxanthin-rich algal meal and vitamin C inhibit Helicobacter pylori infection in BALB/cA mice" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 2000 UNITED STATES, vol. 44, no. 9, 2000, pages 2452-2457, XP008039976 ISSN: 0066-4804 abstract	1-31
Y	MURTHY R ET AL: "Omega-3 fatty acids as anti-inflammatory agents: A classical group of nutraceuticals" JOURNAL OF NUTRACEUTICALS, FUNCTIONAL AND MEDICAL FOODS 1999 UNITED STATES, vol. 2, no. 1, 1999, pages 53-72, XP008039978 ISSN: 1089-4179 abstract	1-31

-/--

INTERNATIONAL SEARCH REPORT

International Application No
T/GB2004/002707

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 03/082313 A (ALCON INC ; KAZHDAN PAVEL (IL); BIODAR LTD (IL); BLATT YOAV (IL); PINT) 9 October 2003 (2003-10-09) page 3, line 3 - line 11 example 3 claim 3	1,3,6, 13-15
E	WO 2004/082399 A (ADVANCED BIONUTRITON CORP ; HAREL MOTI (US); KYLE DAVID J (US); PIECHO) 30 September 2004 (2004-09-30) claims 64,66-72	16-21
E	WO 2004/080196 A (CLAYTON DIANE ; HAREL MOTI (US); ADVANCED BIONUTRITION CORP (US)) 23 September 2004 (2004-09-23) tables 1,2	16-18, 20,21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/002707

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0699437 A	06-03-1996	IT 1274734 B	24-07-1997
		DE 69506642 D1	28-01-1999
		DE 69506642 T2	22-07-1999
		DE 699437 T1	07-11-1996
		EP 0699437 A1	06-03-1996
		JP 8175988 A	09-07-1996
		US 5776978 A	07-07-1998
WO 02102394 A	27-12-2002	WO 02102394 A2	27-12-2002
		CA 2449898 A1	27-12-2002
		EP 1406641 A2	14-04-2004
		JP 2004534800 T	18-11-2004
		US 2004241249 A1	02-12-2004
US 5444054 A	22-08-1995	AT 212194 T	15-02-2002
		AU 689555 B2	02-04-1998
		AU 1884495 A	23-10-1995
		CA 2187628 A1	12-10-1995
		DE 69525150 D1	14-03-2002
		DE 69525150 T2	05-09-2002
		DK 754001 T3	13-05-2002
		EP 0754001 A1	22-01-1997
		ES 2171535 T3	16-09-2002
		HK 1011914 A1	14-02-2003
		NZ 281878 A	24-02-1997
		PT 754001 T	31-07-2002
		WO 9526646 A1	12-10-1995
WO 9837874 A	03-09-1998	SE 522246 C2	27-01-2004
		AT 243030 T	15-07-2003
		AU 719090 B2	04-05-2000
		AU 6295198 A	18-09-1998
		CA 2280715 A1	03-09-1998
		CN 1119994 B	03-09-2003
		DE 69815677 D1	24-07-2003
		WO 9837874 A1	03-09-1998
		EP 0981338 A1	01-03-2000
		IL 131129 A	20-06-2004
		JP 2001517213 T	02-10-2001
		NO 994109 A	27-10-1999
		NZ 337080 A	30-03-2001
		PL 335370 A1	25-04-2000
		SE 9700708 A	28-08-1998
		US 6262316 B1	17-07-2001
WO 0124787 A	12-04-2001	AU 7978800 A	10-05-2001
		CA 2388785 A1	12-04-2001
		EP 1217996 A1	03-07-2002
		JP 2003510353 T	18-03-2003
		WO 0124787 A1	12-04-2001
		US 6773708 B1	10-08-2004
WO 03082313 A	09-10-2003	CA 2479915 A1	09-10-2003
		EP 1487469 A1	22-12-2004
		WO 03082313 A1	09-10-2003
WO 2004082399 A	30-09-2004	WO 2004082399 A2	30-09-2004
		WO 2004082366 A2	30-09-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004080196 A	23-09-2004	WO 2004080196 A2	23-09-2004